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(54) Resolution system.

(57) The invention relates to a process for the kinetic resolution of D,L-racemic mixtures of racemates crystallizing as conglomerates. Resolution is effected from supersaturated solutions of these which is carried out in the presence of a polymer bound inhibitor of crystallization of the one form, resulting in the preferred crystallization of the one form, and when the other form is desired - in the presence of such inhibitor for the other form. Amongst racemic mixtures amenable to this process are amino acids.

The process can be carried out in a two-compartment device, where the compartments are separated by a membrane which is permeable to the constituents of the racemate, while it is impervious to the polymer-bound inhibitor for the crystallization of one of the racemic forms.

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Marshall, Art et al.

Field of the Invention:

The invention relates to a process for the kinetic resolution of D,L-racemic mixtures of racemates which crystallize as conglomerates. The resolution is effected in the presence of a suitable polymeric inhibitor, which consists of a polymer backbone to which there is bound either the D form of the enantiomers (or of a modified compound) when the preferred crystalline form is to be the L-form of the racemate, or an L-form of the enantiomers when the resolved form desired is the D-form. Some of the polymers used for the resolution are novel and form part of the invention. Furthermore, this invention relates to a process of resolution as set out above, where the conglomerate phase is metastable.

Background of the Invention:

It has been demonstrated that kinetic resolution of racemates crystallizing in the form of conglomerates can be accomplished by carrying out the crystallization in the presence of small amounts of resolved additives, the stereochemical molecular structure of which resembles that of one of the enantiomers of the said racemic mixture. According to that process the non-polymeric inhibitors were added in rather large quantities (up to 10% wt/wt of racemic mixture). In addition such additives were occluded in the bulk of the precipitating crystals, in typical amounts of 0.5 - 1.5%. Furthermore, the additive cannot be separated from the precipitating crystals, see U.S. Patent No, 4,533,506, granted August 6, 1985; see also Addadi et al., J.Am.Chem.Soc., 104 4610 (1982).

In the present invention the use of polymeric inhibitors makes it possible to reduce the quantity of the additive by up to a factor of 10 or more.

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The invention relates also to a process of resolution as set out above, where the racemate is provided in adjacent compartments of the resolution cell, separated by a suitable membrane, there being added to the first compartment an inhibitor of D-form crystallization, and to the other compartment an inhibitor of L-form crystallization. The result is that in one compartment essentially pure L-form enantiomer is obtained, and in the other D-form. This is made possible by the fact that contrary to the simple additives used before, the polymeric forms do not pass through such membranes.

The invention also relates to this process of separation where a two-compartment device with a membrane is used and to a separation device for this purpose. Various polymers can be used. As example, the invention is illustrated with reference to certain poly-(^L-acryloyl-L- or -D-amino acid) and poly-(^L-methacryloyl-D- or -L-amino acid) as the compounds which are used as inhibitors, the amino acid bound to the polymer being chosen according to the racemate which is to be resolved.

We have found that addition in solution of poly-(^L-acryloyl-L-lysine) (L-PAL) or poly-(^L-methacryloyl-L-lysine) (L-PMAL) M.W. or poly-[L- α -glutamyl (^L-Acryloyl)hydrazide] (L-PGAH) with different molecular weights in 0.1-1% wt/wt to a supersaturated solution of D,L-glutamic acid.HCl, (Glu.HCl) brings about a preferred crystallization of D-glutamic acid.HCl (D-Glu.HCl). Similarly, addition of poly-(^L-acryloyl -D-lysine) (D-PAL) or the methacryloyl analogue or D-PGAH allows the L-glutamic acid to precipitate. Furthermore, we have found that from a supersaturated aqueous solution of D,L-asparagine (Asn) addition of (L-PAL) or (L-PMAL) allows the

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preferred precipitation of D-asparagine monohydrate; (D-Asn.H₂O) and the addition of D-analogue polymers allows the separation of L-asparagine monohydrate (L-Asn.H₂O). Similarly, the addition of (L-PAL) or (L-PMAL) in 0.1-1% wt/wt to a supersaturated solution of D,L threonine (DL-Thr), brings about preferred crystallization of D-Threonine (D-Thr). Addition of (D-PMAL) or (D-PAL) leads to preferred crystallization of L-threonine (L-Thr).

Analogously, poly-(N-acryloyl-(p-aminobenzoyl)-D-sec-phenethylamide) (D-PA-PAB-PHA) allows the preferential crystallization of L-sec-phenethylalcohol as its 3,5-dinitrobenzoate from a racemic mixture. Inclusion of poly-(N-acryloyl-(p-aminobenzoyl)-L-sec-phenethylamide) (L-PA-AB-PHA) causes the preferred precipitation of the D-form. Analogously, the addition of the poly(P-acrylamido-L-phenyl alanine) (L-PA-PhE) or poly-(acryloxy-L-p-tyrosine) (L-PAO-Tyr) or the corresponding methacryloyl polymers allow the preferential crystallization of D-histidine.HCl.H₂O (D-His.HCl.H₂O) from a racemic mixture both at T > 45°C and T < 45°C, where the conglomerate phase is metastable. Further, the addition of poly-(p-acrylamido-D-phenyl alanine) (D-PA-Phe) or poly-(acryloxy-D-p-tyrosine) (D-PAO-Tyr) or the corresponding methacryloyl polymer allows the preferential crystallization of L-histidine.HClH₂O from the racemic mixture. Similarly, the addition of (L-PAL) or (L-PA-Phe) or (L-PMAL) or (L-PAO-Tyr) or the corresponding methacryloyl polymers allows the preferential crystallization of D-p-hydroxyphenyl-glycine-p-toluene-sulphonate (D-pHPGpTS). The addition of any of the same D polymers results in the preferential crystallization of L-pHPGpTS. In a similar way, the addition of poly-(p-acrylamido-L- α -methyl-phenyl alanine) or

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the corresponding methacryloyl polymer allows the preferential crystallization of D- α -methyl-DOPA (3,4-dihydroxy- α -methyl-phenyl alanine). The addition of any of the same D polymers allows preferential crystallization of L- α -methyl-DOPA.

A similar resolution can be effected by using a device comprising two compartments separated by a membrane, provided with means for agitation. The L-type polymer is in one compartment (A) while the D-type polymer is in the second compartment (B). The polymer cannot diffuse through the membrane while the molecules of the substrate equilibrate (diffuse through the membrane).

Our previous patent, U.S. Patent 4,533,506 describes that racemic conglomerates can be resolved by small molecular weight additives. We have now found that soluble polymers are much more efficient and useful. The fact that the additive is chemically bound to a polymer backbone, taking advantage of the cooperative effect, makes it possible to introduce the polymer in the desired solution in a very reduced amount (up to 1% wt/wt) of the racemic mixture to be resolved. In addition the polymer is not occluded in the crystals but remains in solution. Improved resolution, i.e. high chemical and optical yield of the desired enantiomer is achieved. Since the additive is linked to a polymer of high molecular weight, it allows carrying out the resolution of a racemic mixture in a device of two compartments separated by a membrane.

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EXPERIMENTAL

This invention can be used to produce crystalline threonine, asparagine. H_2O , glutamic acid. HCl , phenethyl alcohol (as its 3,5-dinitrobenzoate), histidine $HCl \cdot H_2O$ and p-hydroxyphenylglycine (as its p-toluenesulphonate salt) enriched in the desired enantiomer, or in its pure enantiomeric form, without requiring the use of seed crystals of this enantiomer. The use of seed crystals of this enantiomer may, however, be desirable from the point of view of the rate of crystallization. For the case where a seed crystal of the desired enantiomer is used, this invention describes an improvement of the process for threonine, asparagine, glutamic acid. HCl , sec-phenethyl alcohol, histidine. $HCl \cdot H_2O$ and pHGPTS by further addition in solution of the appropriate polymers for each compound. The following examples are illustrative to the present invention but are not to be interpreted in a limiting sense.

EXAMPLES 1-23:

Glutamic acid.HCl: D,L glutamic acid (D,L-Glu) (1 g) and poly-(ϵ -N-acryloyl-L-lysine) or poly-(ϵ -N-methacryloyl-L-lysine or poly-[L- ϵ -glutamyl]N-Acryloyl)hydrazide] were heated in hydrochloric acid 5N (5 ml) at about $60^{\circ}C$ to complete dissolution. The solution was filtered, cooled to room temperature with or without agitation and seed crystals (0.5 mg) of D,L-Glu. HCl added. Crystals formed (20 hrs) were separated by filtration and their enantiomeric excess was determined. The conditions and the results are summarized in Tables I and II.

EXAMPLE 24:

An experiment for resolution of D,L-glutamic acid. HCl by a device composed of two compartments separated by a membrane is described. A round perspex piece of 9 cm exterior diameter, 6 cm internal diameter

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and 0.9 cm thickness was connected to another piece of perspex of the same dimensions via a membrane with cut-off of 10000-15000, and mechanically shaken for 48 h. Into each compartment a solution of 4 g D,L-glutamic acid in 20 ml of HCl 5N was introduced (total 8 g/40 ml). Poly-(ϵ -acryloyl-L-lysine) or poly-(ϵ -methacryloyl-L-lysine) was dissolved in one compartment (A) while poly-(ϵ -acryloyl-D-lysine) or poly-(ϵ -methacryloyl-D-lysine) was dissolved in the second compartment (B). Each compartment was seeded with 0.5 mg of D,L-glutamic acid.HCl. After 48 h the solid from each compartment was filtered to give from compartment (A) 605 mg of D-glutamic acid.HCl with (Δ)D = -24°C and from compartment (B) 575 mg of L-glutamic acid.HCl with (Δ)D = +24°C.

EXAMPLES 25-29

Asparagine.H₂O: A slurry of D,L-Asn.H₂O (500 mg) and poly-(ϵ -methacryloyl-L-lysine) in water (5 ml) was heated to about 80°C until complete dissolution occurred. The warm solution was filtered and cooled to room temperature without agitation. After 20 h the separated crystals were recovered by filtration and the enantiomeric excess was determined. The conditions and results are summarized in Table III.

EXAMPLES 30-38

Threonine: D,L-Threonine (DL-Thr) and poly-(ϵ -methacryloyl-L-lysine) or poly-(ϵ -acryloyl-L-lysine) were heated in water to about 80°C until complete dissolution occurred. The hot solution was filtered and cooled to room temperature. After a defined time the precipitate was filtered and the enantiomeric excess was determined. The conditions and results are summarized in Table IV.

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EXAMPLE-39-48

3,5-Dinitro-sec-Phenethyl Benzoate: A solution of 3,5-dinitro-DL-sec-phenethylbenzoate in toluene and a solution of poly-(N-acryloyl-(*p*-amino-benzoyl)-D-sec-phenethylamide) or the poly-L-analogue in N,N'-dimethyl-formamide were mixed together, heated to complete dissolution, and seed crystals of 3,5-dinitro-DL-sec-phenethylbenzoate (0.5 mg) added. The crystals which were formed were separated by filtration, dried and the enantiomeric excess was determined. The results and conditions are summarized in Table V.

EXAMPLES 49-59:

Histidine.HCl.H₂O: D,L-His.HCl.H₂O (3.2 g) and the appropriate polymer were slurried in water (5 ml) and the slurry was heated to complete dissolution. The hot solution was filtered and allowed to stand at 50°C for 20 hrs without agitation. The crystals were collected by filtration and the enantiomeric excess was determined. The results are summarized in Table VI.

EXAMPLES 60-67:

Histidine. HCl.H₂O: D,L-His.HCl.H₂O (4.0 g) and the appropriate polymer were slurried in water (10 ml) and the slurry was heated to complete dissolution. The hot solution was filtered, cooled to 25°C, seeded and allowed to stand without agitation for 3-7 days. The crystals were collected by filtration and the enantiomeric excess was determined. The results are summarized in Table VII.

EXAMPLES 68-76:

pHPGpTS: D,L-pHPGpTS and the appropriate polymer were slurried in 0.5 M *p*-toluenesulfonic acid in water, and the slurry was heated until

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complete solution occurred. The hot solution was filtered and allowed to cool to room temperature without agitation. The crystals were collected by filtration and the enantiomeric excess was determined. The conditions and results are summarized in Table VIII.

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Table I: (Glu.HCl). The following examples were carried out without agitation:

Example	type of polymer	weight* ¹ (%) of polymer	[α]D degree	precipitated crystals e.e. (%)	chemical* ² yield %
1	L-PMAL	3	-23.3	94.7	22.5
2	"	3	-23.7	96.3	25.2
3	"	2	-24.2	98.4	22.0
4	"	1	-23.2	94.3	26.6
5	"	1	-24.0	97.5	21.6
6	"	0.5	-24.2	98.4	22.0
7	"	0.5	-23.8	96.7	20.3
8	"	0.1	-23.6	95.9	26.5
9	"	0.1	-11.8	47.9	33.6
10	"	0.1	-10.2	41.4	37.2
11	L-PAL	3	-24.0	97.5	15.3
12	"	1	-23.8	96.7	12.5
13	"	0.5	-23.3	94.7	16.1
14	"	0.1	-23.8	96.7	11.6
15	D-PAL	0.5	+22.9	93.0	15.7
16	"	0.1	+23.7	96.3	19.3
17	L-PGAH	1.0	-23.7	96.3	18.0
18	"	0.8	-24.2	98.4	10.0
19	"	0.5	-24.2	98.4	12.0
20	D-PGAH	0.8	-24.0	97.5	18.0
21	"	0.5	-24.2	98.4	18.0

*¹ expressed in weight % of racemic glutamic acid. HCl. This same notation (weight % of racemic material) is used in all the following tables.

*² the chemical yield is defined as; $\frac{\text{precipitate}}{\text{total racemic mixture}}$ This same notation is used in all the following tables.

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Table II: The following experiments were carried out with agitation (magnetic stirring).

Example	type of polymer	weight (%) of polymer	[α] D degree	precipitated crystals e.e. (%)	chemical yield %
22	L-PMAL	1	-24.2	98.3	20.4
23	"	1	-24.0	97.5	22.0

Table III - (Asn.H₂O)

Example	weight% of polymer	[α] D degree	precipitated crystals e.e. of	chemical yield %	conditions seeded with 0.5mg of
25	0.2	- 4.3	14	52.2	DL-Asn.H ₂ O
26	1	- 9.0	29.5	45.0	DL-Asn.H ₂ O
27	2	-28.3	92.7	14.6	D-Asn.H ₂ O
28	4	-12.0	39.3	40.0	DL-Asn.H ₂ O
29	4	-27.7	90.8	15.6	D-Asn.H ₂ O

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TABLE IV: (Thr) The following experiments were carried out with D,L seed crystals (0.5 mg):

Example*	DL-Thr (gr)	Vol. of H ₂ O (ml)	Weight % of Poly-(N-metha- croyl-L-lysine)	time h.	[α] _D degree	precipitated crystals e.e.	chemical yield %
30	0.9	3	3.3	20	+15.0	95.3	23.1
31	1.5	5	1.3	20	+26.6	94.6	27.6
32	0.9	3	1.1	6	+25.7	91.7	12.6
33	1.5	5	1.1	20	+26.9	96.0	18.4
34	0.9	3	0.5	6	+25.3	90.3	10.0
35	0.9	3	0.5	20	+ 8.0	28.5	34.2
36	1.5	5	0.3	20	+25.8	92.1	19.0
37	0.9	3	0.5	20	+22	78.5	22.2
38	0.9	3	1	20	+23.9	85.3	19.6

* Experiments 30-36 were carried out without agitation and experiments 37-38 with agitation.

TABLE V: (3,5-Dinitro-D,L-sec-phenethyl benzoate)

Example	wt. (gr) of DL- substr.	ol. of toluene (ml)	Vol. of DMF (ml)	Polym. config. (%)	time h	W/D crystals- degree	precipitated crystals- e.e.	chemical yield %
39	1.4	0.5	1	D	2	5	+37.5	97.4
40	1.5	0.5	1	D	1	7.5	+38.5	100
41	1.5	0.5	1	D	1	11	+33.5	87
42	1.5	0.5	1.5	D	3	24	+38.5	100
43	1.5	0.5	1	D	0.2	5	+ 5	13
44	4.5	0.5	3	D	1	8	+38.5	100
45	1.5	0.5	1	L	None	3.5	0	22
46	1.5	0.5	1	L	1	7	-38.5	100
47	1.5	0.5	1.5	L	2	18	-38.5	100
48	1.5	0.5	1	L	1.5	6	-38.0	98

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TABLE VI: (His.HCl.H₂O)

Example	wt % of polymer	type of polymer	polym. config.	seeding with	[α]D degree	precipitated crystals	e.e.	chemical yield %
49	1	PA-Phe	L	No	-8.8	91.6	6.9	
50	1	"	L	D-His.HCl.H ₂ O	-9.6	100	10	
51	1	"	L	D-His.HCl.H ₂ O	-9.1	94.7	11	
52	1	"	D	L-His.HCl.H ₂ O	+9.6	100	10	
53	1	PAO-Tyr	L	D-His.HCl.H ₂ O	-9.6	100	8.4	
54	1	"	L	D-His.HCl.H ₂ O	-9.6	100	8.3	
55	1	"	D	L-His.HCl.H ₂ O	+9.2	95.8	8.5	
56	0	-	-	D-His.HCl.H ₂ O	-0.9	9.3	11	
57	0	-	-	L-His.HCl.H ₂ O	+0.8	8.3	10.3	
58	10	PMAL	L	D-His.HCl.H ₂ O	-4.8	50	19.0	
59	10	PMAL	D	L-His.HCl.H ₂ O	+5.8	50	12.0	

TABLE VII: (His.HCl.H₂O)

Example	wt% of polymer	type of polymer	Polym. config.	seeding with	[α]D degree	precipitated crystals	e.e.%	chemical yield(%)
		polymer						
60	2	PA-Phe	L	D-His.HCl.H ₂ O	-9.6	100		15
61	2	PA-Phe	D	L-His.HCl.H ₂ O	+9.6	100		15
62	2	PAO-Tyr	L	D-His.HCl.H ₂ O	-9.6	100		15
63	2	PAO-Tyr	D	L-His.HCl.H ₂ O	+9.6	100		15
64	3	PA-Phe	L	DL-His.HCl.H ₂ O	-9.6	100		13
65	3	PA-Phe	D	DL-His.HCl.H ₂ O	+9.6	100		13
66	3	PAO-Tyr	L	DL-His.HCl.H ₂ O	-9.6	100		13
67	3	PAO-Tyr	D	DL-His.HCl.H ₂ O	+9.6	100		13

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TABLE VIII: (PHPGpTS)

Example	D L weight PHPGpTS, gr/ml *	% of polymer	type of polymer	polym config	seeding with	Time h	[α] degree	precipitated crystals	e.e.	chemical yield%
68	0.4/2	1.2	PMAL	L	No	20	-65.7	97.6	13.2	
69	0.4/2	5	"	D	No	20	+65	96.5	12.2	
70	0.5/2	2.5	"	L	No	20	-38.5	57.2	25.8	
71	0.5/2	2.5	"	L	D-PHPGpTS	20	-24.0	35.7	32.4	
72	0.5/2	2.5	"	L	"	20	-59.7	88.7	22.8	
73	1.4/4	1	PA-Phe	L	"	2	-66	96.0	16.5	
74	1.4/4	1	"	D	L-PHPGpTS	2	+67.2	99.8	10.0	
75	1.4/4	1.5	"	L	DL-	"	2	-25	37.1	27
76	1.4/4	1	"	L	DL-	"	2	-33	49.0	21

* A solution of 0.5N of p-toluenesulfonic acid in water.

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Claims:

1. A process for the kinetic resolution of D,L racemic mixtures of compounds crystallizing in the form of conglomerates from supersaturated solutions of same which comprises effecting the crystallization in the presence of an effective quantity of a polymer-bound inhibitor of the crystallization of the one form, thus promoting the preferred crystallization of the other form.
2. A process according to claim 1, where the conglomerate form is metastable and the polymer is an inhibitor of the stable racemic form as well.
3. A process according to claim 1 or 2 , where the D,L racemic mixture is one of an amino acid.
4. A process according to claim 1, 2 or 3, where the inhibitor, an amino acid bound to a polymer, is one of the enantiomers of the racemic mixture to be separated, a chemical modification thereof or another moiety known to inhibit crystallization of one of the enantiomers.
5. A process according to any of claims 1 to 4, where the polymer is a poly-N^L-acryloyl or poly-N^L-methacryloyl polymer, to which the inhibiting moiety is linked.
6. A process according to any of claims 1 to 5, whenever effected in a system comprising two compartments separated by a membrane permeable to the constituents of the racemate, yet impermeable to the polymer-bound moieties, where in one compartment there is located an inhibitor for the crystallization of the L-form, and in the other an inhibitor for the crystallization of the D-form, said inhibitors being polymer-bound inhibiting moieties.

7. A process according to any of claims 1 to 6, for resolution of a mixture of D- and L-glutamic acid hydrochloride material which comprises forming a supersaturated solution of said mixture, adding poly-(N-acryloyl-L-lysine) or poly-(^EN-methacryloyl-L-lysine) or poly-[L- α -glutamyl-(N-acryloyl)hydrazide] as an inhibitor of the L-amino acid when D-amino acid is desired, or a similar additive in the D-form when L-form is desired, and crystallizing part of the compound from said supersaturated solution.
8. A process according to claim 7, wherein also seed crystals of the desired form of Glu.HCl are added during the crystallization step.
9. A process according to claim 7 or 8 whenever executed in a membrane-separated two-compartment system.
10. A process according to any of claims 1 to 6, for resolution of a mixture of D- and L-forms of asparagine, which comprises forming a supersaturated solution of said mixture, adding polymer-bound L-lysine as crystallization inhibitor of the L-form of asparagine when the D-form of asparagine is desired, or including the D-form of these polymers when the L-form of asparagine is desired, and crystallizing a portion of the asparagine from said supersaturated solution.
11. A process according to claim 10, where, in addition seeds of asparagine of the desired form are added to said supersaturated solution.
12. A process according to any of claims 1 to 6 for the resolution of a mixture of D- and L-form of threonine which comprises

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forming a supersaturated solution of said mixture adding polymer bound L-lysine as crystallization inhibitor of the L-form of threonine when the D-form of threonine is desired, or including the D-form of the polymer when the L-form of threonine is desired, and crystallizing a portion of the threonine from said supersaturated solution.

13. A process according to claim 12, where in addition seeds of threonine of the desired form are added to said supersaturated solution.
14. A process according to any of claims 1 to 6, for resolution of a mixture of D- and L-Histidine HCl which comprises forming a supersaturated solution of said mixture, adding polymer bound L-lysine or polymer bound p-amino-L-phenyl alanine or polymer bound L-p-tyrosine as an inhibitor of the L-amino acid when the D-amino acid is desired or a similar polymeric additive in the D-form when the L-form is desired, and crystallizing part of the compound from said supersaturated solution, at a temperature of 45⁰C or above.
15. A process according to claim 2, for resolution of a mixture of D- and L- Histidine HCl which comprises forming a supersaturated solution of said mixture, adding polymer bound p-amino-L-phenyl alanine or polymer bound L-p-tyrosine as an inhibitor of L amino acid when the D-amino acid is desired or a similar polymeric additive in D-form when the L-form is desired, and crystallizing part of the compound from said supersaturated solution at a temperature of 45⁰C or below.

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16. A process according to any of claims 14 or 15, wherein also seed crystals of the desired form of His.HCl.H₂O are added during the crystallization step.
17. A process according to any of claim 1 to 6, for a resolution of a mixture of D and L-pHPGpTS which comprises forming a supersaturated solution of said mixture, adding polymer bound L-lysine or polymer bound p-amino-L-phenyl alanine or polymer bound L-p-tyrosine as an inhibitor of the L-amino acid when the D-amino acid is desired, or a similar polymeric additive in the D-form when the L-form is desired, and crystallizing part of the compound from said supersaturated solution.
- 18 A process according to claim 17, wherein also seed crystals of the desired form of pHPGpTS are added during the crystallization step.
19. A process according to any of claims 1 to 6, for resolution of a mixture of D-and L-forms of 3,5-dinitro-sec-phenethylbenzoate, which comprises forming a supersaturated solution of said mixture, adding poly-[N-acryloyl-(p-aminobenzoyl)-D-sec-phenethylamide] or the methacryloyl analogue as crystallization inhibitor of D-form of 3,5-dinitro-sec-phenethylbenzoate when L-form is desired, or including the L-forms of these polymers when D-form of 3,5-dinitro-sec-phenethylbenzoate is desired and crystallizing a portion from said supersaturated solution.
20. A process according to any of claims 7, 10, 12, 14, 17 or 19, where the polymer bound form used is poly-(^EN-acryloyl) lysine or poly(^EN-methacryloyl)-L-lysine or a corresponding polymer, as defined in the specific claims.

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Chiral soluble polymers
21./for use in the resolution according to claim 1, of racemic
mixtures of enantiomers, containing a
specific entity which retards the crystallization of one of the
enantiomers.

22. A chiral soluble polymer according to claim 21, of the form of
poly-(N-acryloyl-L- or D-amino acid) or poly-(N-methacryloyl-L-
or D-amino acid), where said amino acid is adapted to retard the
crystallization of one of the enantiomers of the mixture to be
resolved.

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EUROPEAN SEARCH REPORT

Application number

EP 86 11 5704

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	DE-A-2 458 066 (MITSUBISHI RAYON) * Claims 1,9; table II, no. 9 *	21,22	C 07 B 57/00 C 07 C 101/02 C 07 C 103/18 C 07 D 233/64 C 07 C 79/46 C 07 C 99/12 C 08 F 20/60
A	DE-A-3 122 537 (YEDA RESEARCH AND DEVELOPMENT) * Claims; examples *	1-18, 20	
A	US-A-2 790 001 (J.L. PURVIS) * Claims *	1-18, 20	
A	US-A-2 937 200 (H.L. FIKE) * Claims *	1-18, 20	
	-----		TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 B 57/00 C 07 C 99/00 C 07 C 101/00 C 08 F 20/00
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	19-02-1987	WRIGHT M.W.	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone	T : theory or principle underlying the invention		
Y : particularly relevant if combined with another document of the same category	E : earlier patent document, but published on, or after the filing date		
A : technological background	D : document cited in the application		
O : non-written disclosure	L : document cited for other reasons		
P : intermediate document	R : member of the same patent family, corresponding document		



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Description**Field of the Invention:**

5 The invention relates to a process for the kinetic resolution of D,L-racemic mixtures of racemates which crystallize as conglomerates. The resolution is effected in the presence of a suitable polymeric inhibitor, which consists of a polymer backbone to which there is bound either the D form of the enantiomers (or of a modified compound) when the preferred crystalline form is to be the L-form of the racemate, or an L-form of the enantiomers when the resolved form desired is the D-form. Some of the polymers used for the resolution are 10 novel and form part of the invention. Furthermore, this invention relates to a process of resolution as set out above, where the conglomerate phase is metastable.

15 Background of the Invention:

It has been demonstrated that kinetic resolution of racemates crystallizing in the form of conglomerates can be accomplished by carrying out the crystallization in the presence of small amounts of resolved additives, the 20 stereochemical molecular structure of which resembles that of one of the enantiomers of the said racemic mixture. According to that process the non-polymeric inhibitors were added in rather large quantities (up to 10 % wt/wt of racemic mixture). In addition such additives were occluded in the bulk of the precipitating crystals, in typical amounts of 0.5 - 1.5 %. Furthermore, the additive cannot be separated from the precipitating crystals, see U.S. Patent No. 4 533 506, granted August 6, 1985; see also Addadi et al., J. Am. Chem. Soc., 104 4610 (1982).

25 In the present invention the use of polymeric inhibitors makes it possible to reduce the quantity of the additive by up to a factor of 10 or more.

The invention relates also to a process of resolution as set out above, where the racemate is provided in adjacent compartments of the resolution cell, separated by a suitable membrane, there being added to the first compartment an inhibitor of D-form crystallization, and to the other compartment an inhibitor of L-form crystallization. The result is that in one compartment essentially pure L-form enantiomer is obtained, and in the other D-form. This is made possible by the fact that contrary to the simple additives used before, the polymeric forms do not pass through such membranes.

The invention also relates to this process of separation where a two-compartment device with a membrane is used and to a separation device for this purpose. Various polymers can be used. As example, the invention is 35 illustrated with reference to certain poly-(N^c-acryloyl-L- or -D-amino acid) and poly-(N^c-methacryloyl-D- or -L-amino acid) as the compounds which are used as inhibitors, the amino acid bound to the polymer being chosen according to the racemate which is to be resolved.

We have found that addition in solution of poly-(N^c-acryloyl-L-lysine) (L-PAL) or poly-(N^c-methacryloyl-L-lysine) (L-PMAL) or poly-[L- α -glutamyl]N-Acryloyl]hydrazide] (L-PGAH) with different molecular weights in 0.1 40 - 1 % wt/wt to a supersaturated solution of D,L-glutamic acid.HCl, (Glu.HCl) brings about a preferred crystallization of D-glutamic acid.HCl (D-Glu.HCl). Similarly, addition of poly-(N^c-acryloyl-D-Lysine) (D-PAL) or the methacryloyl analogue of D-PGAH allows the L-glutamic acid to precipitate. Furthermore, we have found that from a supersaturated aqueous solution of D,L-asparagine (Asn) addition of (L-PAL) or (L-PMAL) allows the preferred precipitation of D-asparagine monohydrate, (D-Asn.H₂O) and the addition of D-analogue 45 polymers allows the separation of L-asparagine monohydrate (L-Asn.H₂O). Similarly, the addition of (L-PAL) or (L-PMAL) in 0.1 - 1 % wt/wt to a supersaturated solution of D,L threonine (DL-Thr), brings about preferred crystallization of D-Threonine (D-Thr). Addition of (D-PMAL) or (D-PAL) leads to preferred crystallization of L-threonine (L-Thr).

Analogously, poly-(N-acryloyl-(p-aminobenzoyl)-D-sec-phenethylamide) (D-PA-PAB-PHA) allows the preferential crystallization of L-sec-phenethylalcohol as its 3,5-dinitrobenzoate from a racemic mixture. Inclusion of poly-(N-acryloyl-(p-aminobenzoyl)-L-sec-phenethylamide) (L-PA-PAB-PHA) causes the preferred precipitation of the D-form. Analogously, the addition of the poly(P-acrylamido-L-phenyl alanine) (L-PA-PhE) or poly-(acryloxy-L-p-tyrosine) (L-PAO-Tyr) or the corresponding methacryloyl polymers allow the preferential crystallization of D-histidine.HCl.H₂O (D-His.HCl.H₂O) from a racemic mixture both at T > 45°C and T < 45°C, 55 where the conglomerate phase is metastable. Further, the addition of poly-(P-acrylamido-D-phenyl alanine) (D-PA-Phe) or poly-(acryloxy-D-p-tyrosine) (D-PAO-Tyr) or the corresponding methacryloyl polymer allows the preferential crystallization of L-histidine.HCl.H₂O from the racemic mixture. Similarly, the addition of (L-PAL) or (L-PA-Phe) or (L-PMAL) or (L-PAO-Tyr) or the corresponding methacryloyl polymers allows the preferential crystallization of D-p-hydroxphenyl-glycine-p-toluenesulphonate (D-pHPGpTS). The addition of any of the 60 same D polymers results in the preferential crystallization of L-pHPGpTS. In a similar way, the addition of poly-(P-acrylamido-L- α -methyl-phenyl alanine) or the corresponding methacryloyl polymer allows the preferential crystallization of D- α -methyl-DOPA (3,4-dihydroxy- α -methyl-phenyl alanine). The addition of any of the same D polymers allows preferential crystallization of L- α -methyl-DOPA.

A similar resolution can be effected by using a device comprising two compartments separated by a 65 membrane, provided with means for agitation. The L-type polymer is in one compartment (A) while the D-type

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polymer is in the second compartment (B). The polymer cannot diffuse through the membrane while the molecules of the substrate equilibrate (diffuse through the membrane).

Our previous patent, U.S. Patent 4 533 506 describes that racemic conglomerates can be resolved by small molecular weight additives. We have now found that soluble polymers are much more efficient and useful. The fact that the additive is chemically bound to a polymer backbone, taking advantage of the cooperative effect, makes it possible to introduce the polymer in the desired solution in a very reduced amount (up to 1 % wt/wt) of the racemic mixture to be resolved. In addition the polymer is not occluded in the crystals but remains in solution. Improved resolution, i.e. high chemical and optical yield of the desired enantiomer is achieved. Since the additive is linked to a polymer of high molecular weight, it allows carrying out the resolution of a racemic mixture in a device of two compartments separated by a membrane.

Experimental

This invention can be used to produce crystalline threonine, asparagine.H₂O, glutamic acid.HCl, phenethyl alcohol (as its 3,5-dinitrobenzoate), histidine HCl.H₂O and p-hydroxyphenylglycine (as its p-toluenesulphonate salt) enriched in the desired enantiomer, or in its pure enantiomeric form, without requiring the use of seed crystals of this enantiomer. The use of seed crystals of this enantiomer may, however, be desirable from the point of view of the rate of crystallization. For the case where a seed crystal of the desired enantiomer is used, this invention describes an improvement of the process for threonine, asparagine, glutamic acid.HCl, sec-phenethyl alcohol, histidine.HCl.H₂O and pHGPPTS by further addition in solution of the appropriate polymers for each compound. The following examples are illustrative to the present invention but are not to be interpreted in a limiting sense.

25

Examples 1 - 23:

30 Glutamic acid.HCl: D,L glutamic acid (D,L-Glu) (1 g) and poly-(N^c-acryloyl-L-lysine) or poly-(N^c-methacryloyl-L-lysine or poly-[L-glutamyl]N-Acryloyl)hydrazide] were heated in hydrochloric acid 5N (5 ml) at about 60°C to complete dissolution. The solution was filtered, cooled to room temperature with or without agitation and seed crystals (0.5 mg) of D,L-Glu.HCl added. Crystals formed (20 hrs) were separated by filtration and their enantiomeric excess was determined. The conditions and the results are summarized in Tables I and II.

35

Example 24:

40 An experiment for resolution of D,L-glutamic acid.HCl by a device composed of two compartments separated by a membrane is described. A round perspex piece of 9 cm exterior diameter, 6 cm internal diameter and 0.9 cm thickness was connected to another piece of perspex of the same dimensions via a membrane with cut-off of 10 000 - 15 000, and mechanically shaken for 48 h. Into each compartment a solution of 4 g D,L-glutamic acid in 20 ml of HCl 5N was introduced (total 8 g/40 ml). Poly-(N^c-acryloyl-L-lysine) or poly-(N^c-methacryloyl-L-lysine) was dissolved in one compartment (A) while poly-(N^c-acryloyl-D-lysine) or poly-(N^c-methacryloyl-D-lysine) was dissolved in the second compartment (B). Each compartment was seeded with 0.5 mg of D,L-glutamic acid.HCl. After 48 h the solid from each compartment was filtered to give from compartment (A) 605 mg of D-glutamic acid.HCl with (α)D = -24°C and from compartment (B) 575 mg of L-glutamic acid.HCl with (α)D = +24°C.

50

Examples 25 - 29:

55 Asparagine.H₂O: A slurry of D,L-Asn.H₂O (500 mg) and poly-(N^c-methacryloyl-L-lysine) in water (5 ml) was heated to about 80°C until complete dissolution occurred. The warm solution was filtered and cooled to room temperature without agitation. After 20 h the separated crystals were recovered by filtration and the enantiomeric excess was determined. The conditions and results are summarized in Table III.

60

Examples 30 - 38

65 Threonine: D,L-Threonine (DL-Thr) and poly-(N^c-methacryloyl-L-lysine) or poly-(N^c-acryloyl-L-lysine) were heated in water to about 80°C until complete dissolution occurred. The hot solution was filtered and cooled to

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room temperature. After a defined time the precipitate was filtered and the enantiomeric excess was determined. The conditions and results are summarized in Table IV.

5

Example 39 - 48:

10 3,5-Dinitro-sec-Phenethyl Benzoate: A solution of 3,5-dinitro-DL-sec-phenethylbenzoate in toluene and a formamide were mixed together, heated to complete dissolution, and seed crystals of 3,5-dinitro-DL-sec-phenethylbenzoate (0.5 mg) added. The crystals which were formed were separated by filtration, dried and the enantiomeric excess was determined. The results and conditions are summarized in Table V.

15

Examples 49 - 59:

20 Histidine.HCl.H₂O: D,L-His.HCl.H₂O (3.2 g) and the appropriate polymer were slurried in water (5 ml) and the slurry was heated to complete dissolution. The hot solution was filtered and allowed to stand at 50°C for 20 hrs without agitation. The crystals were collected by filtration and the enantiomeric excess was determined. The results are summarized in Table VI.

25

Examples 60 - 67:

30 Histidine.HCl.H₂O: D,L-His.HCl.H₂O (4.0 g) and the appropriate polymer were slurried in water (10 ml) and the slurry was heated to complete dissolution. The hot solution was filtered, cooled to 25°C, seeded and allowed to stand without agitation for 3 - 7 days. The crystals were collected by filtration and the enantiomeric excess was determined. The results are summarized in Table VII.

Examples 68 - 76:

35

40 pHPGpTS: D,L-pHPGpTS and the appropriate polymer were slurried in 0.5 M p-toluenesulfonic acid in water, and the slurry was heated until complete solution occurred. The hot solution was filtered and allowed to cool to room temperature without agitation. The crystals were collected by filtration and the enantiomeric excess was determined. The conditions and results are summarized in Table VIII.

Table I: (Glu.HCl. The following examples were carried out without agitation:

45	Example	type of polymer	weight*1 (%) of polymer	[α] D degree	precipitated crystals e.e. (%)	chemical*2 yield %
	1	L-PMAL	3	-23.3	94.7	22.5
	2	"	3	-23.7	96.3	25.2
	3	"	2	-24.2	98.4	22.0
50	4	"	1	-23.2	94.3	26.6
	5	"	1	-24.0	97.5	21.6
	6	"	1	-24.2	98.4	22.0
	7	"	0.5	-23.8	96.7	20.3
	8	"	0.5	-23.6	95.9	26.5
55	9	"	0.1	-11.8	47.9	33.6
	10	"	0.1	-10.2	41.4	37.2
	11	L-PAL	3	-24.0	97.5	15.3
	12	"	1	-23.8	96.7	12.5
	13	"	0.5	-23.3	94.7	16.1
60	14	"	0.1	-23.8	96.7	11.6
	15	D-PAL	0.5	+22.9	93.0	15.7
	16	"	0.1	+23.7	96.3	19.3
	17	L-PGAH	1.0	-23.7	96.3	18.0
	18	"	0.8	-24.2	98.4	10.0
65	19	"	0.5	-24.2	98.4	12.0

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20	D-PGAH	0.8	-24.0	97.5	18.0
21		0.5	-24.2	98.4	18.0

5 *1 expressed in weight % of racemic gluamic acid. HCl. This same (weight % of recemic material) is used in all the following tables.

*2 the chemical yield is defined as; $\frac{\text{precipitate}}{\text{total racemic mixture}}$. This same notation is used in all the following tables.

Table II: The following experiments were carried out with agitation (magnetic stirring)

Example	type of polymer	weight*1 (%) of polymer	[α] D degree	precipitated crystals e.e. (%)	chemical*2 yield %
22	L-PMAL	1	-24.2	98.3	20.4
15	23	1	-24.0	97.5	22.0

Table III: (Asn.H₂O)

Example	weight % of polymer	[β] D degree	precipitated crystals e.e. of	chemical yield %	conditions seeded with 0.5 mg of
25	0.2	- 4.3	14	52.2	DL-Asn.H ₂ O
26	1	- 9.0	29.5	45.0	DL-Asn.H ₂ O
27	2	-28.3	92.7	14.6	D-Asn.H ₂ O
28	4	-12.0	39.3	40.0	DL-Asn.H ₂ O
29	4	-27.7	90.8	15.6	D-Asn.H ₂ O

Table IV: (Thr). The following experiments were carried out with D,L seed crystals (0.5 mg):

Example	DL-Thr (gr)	Vol. of H ₂ O (ml)	Weight % of Poly-(N-metha- cryloy-L-lysine)	time h	[α]D degree	precipitated crystals e.e.	chemical yield %
30	0.9	3	3.3	20	+ 15.0	95.3	23.1
31	1.5	5	1.3	20	+ 26.6	94.6	27.6
32	0.9	3	1.1	6	+ 25.7	91.7	12.6
33	1.5	5	1.1	20	+ 26.9	96.0	18.4
34	0.9	3	0.5	6	+ 25.3	90.3	10.0
35	0.9	3	0.5	20	+ 8.0	28.5	34.2
36	1.5	5	0.3	20	+ 25.8	92.1	19.0
37	0.9	3	0.5	20	+ 22	78.5	22.2
45	38	0.9	3	1	20	+ 23.9	85.3

** Experiments 30 - 36 were carried out without agitation and experiments 37 - 38 with agitation.

Table V: (3,5-Dinitro-D,L-sec-phenethyl benzoate)

Example	wt. (gr) of DL- substr.	ol. of toluene (ml)	Vol. of DMF (ml)	Polym. config.	Weight (%) of polym.	time h	[α]D degree	precipitated crystals e.e.	chemical yield %
55	39	1.4	0.5	D	2	5	+37.5	97.4	6.4
	40	1.5	0.5	1	D	1	+38.5	100	10
	41	1.5	0.5	1	D	1	+33.5	87	15
	42	1.5	0.5	1.5	D	3	+38.5	100	14
	43	1.5	0.5	1	D	0.2	+ 5	13	8.6
60	44	4.5	0.5	3	D	1	+38.5	100	11.2
	45	1.5	0.5	1	None	3.5	0	0	22
	46	1.5	0.5	1	L	1	-38.5	100	9.5
	47	1.5	0.5	1.5	L	2	-38.5	100	11
65	48	1.5	0.5	1	L	1.5	-38.0	98	7

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Table VI: (His.HCl.H₂O)

5	Example	wt % of polymer	type of polymer	polym. config.	seeding with	[α]D degree	precipitated crystals e.e.	chemical yield %
10	49	1	PA-Phe	L	no	-8.8	91.6	6.9
	50	1	-	L	D-His.HCl.H ₂ O	-9.6	100	10
	51	1	-	L	D-His.HCl.H ₂ O	-9.1	94.7	11
	52	1	-	D	L-His.HCl.H ₂ O	+9.6	100	10
15	53	1	PAO-Tyr	L	D-His.HCl.H ₂ O	-9.6	100	8.4
	54	1	-	L	D-His.HCl.H ₂ O	-9.6	100	8.3
	55	1	-	D	L-His.HCl.H ₂ O	+9.2	95.8	8.5
	56	0	-	-	D-His.HCl.H ₂ O	-0.9	9.3	11
20	57	0	-	-	L-His.HCl.H ₂ O	+0.8	8.3	10.3
	58	10	PMAL	L	D-His.HCl.H ₂ O	-4.8	50	19.0
	59	10	PMAL	D	L-His.HCl.H ₂ O	+5.8	50	12.0

Table VII: (His.HCl.H₂O)

20	Example	wt % of polymer	type of polymer	polym. config.	seeding with	[α]D degree	precipitated crystals e.e. %	chemical yield %
25	60	2	PA-Phe	L	D-His.HCl.H ₂ O	-9.6	100	15
	61	2	PA-Phe	D	L-His.HCl.H ₂ O	+9.6	100	15
	62	2	PAO-Tyr	L	D-His.HCl.H ₂ O	-9.6	100	15
	63	2	PAO-Tyr	D	L-His.HCl.H ₂ O	+9.6	100	15
30	64	3	PA-Phe	L	DL-His.HCl.H ₂ O	-9.6	100	13
	65	3	PA-Phe	D	DL-His.HCl.H ₂ O	+9.6	100	13
	66	3	PAO-Tyr	L	DL-His.HCl.H ₂ O	-9.6	100	13
	67	3	PAO-Tyr	D	DL-His.HCl.H ₂ O	+9.6	100	13

Table VIII: (PHPGpTS)

35	Example	D L PHpGpTS, gr/ml*	weight % of polymer	type of polymer	polym. config.	seeding with	time h	[α] degree	precipitated crystals e.e.	chemical yield %
40	68	0.4/2	1.2	PMAL	L	No	20	-65.7	97.6	13.2
	69	0.4/2	5	-	D	No	20	+65	96.5	12.2
	70	0.5/2	2.5	-	L	No	20	-38.5	57.2	25.8
	71	0.5/2	2.5	-	L	D-PHPGpTS	20	-24.0	35.7	32.4
45	72	0.5/2	2.5	-	L	-	20	-59.7	88.7	22.8
	73	1.4/4	1	PA-Phe	L	-	2	-66	98.0	16.5
	74	1.4/4	1	-	D	L-PHPGpTS	2	+67.2	99.8	10.0
	75	1.4/4	1.5	-	L	DL-PHPGpTS	2	-25	37.1	27
	76	1.4/4	1	-	L	DL-PHPGpTS	2	-33	49.0	21

* A solution of 0.5N of p-toluenesulfonic acid in water.

50

Claims

1. A process for the kinetic resolution of D,L racemic mixtures of compounds crystallizing in the form of conglomerates from supersaturated solutions of same which comprises effecting the crystallization in the presence of an effective quantity of a polymer-bound inhibitor of the crystallization of the one form, thus promoting the preferred crystallization of the other form.
2. A process according to claim 1, where the conglomerate form is metastable and the polymer is an inhibitor of the stable racemic form as well.
3. A process according to claim 1 or 2, where the D,L racemic mixture is one of an amino acid.
4. A process according to claim 1, 2 or 3, where the inhibitor, an amino acid bound to a polymer, is one of the enantiomers of the racemic mixture to be separated, a chemical modification thereof or another moiety known to inhibit crystallization of one of the enantiomers.
5. A process according to any of claims 1 to 4, where the polymer is a poly-N^c-acryloyl or poly-N^c-methacryloyl polymer, to which the inhibiting moiety is linked.

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6. A process according to any of claims 1 to 5, whenever effected in a system comprising two compartments separated by a membrane permeable to the constituents of the racemate, yet impermeable to the polymer-bound moieties, where in one compartment there is located an inhibitor for the crystallization of the L-form, and in the other an inhibitor for the crystallization of the D-form, said inhibitors being polymer-bound inhibiting moieties.

5 7. A process according to any of claims 1 to 6, for resolution of a mixture of D- and L-glutamic acid hydrochloride material which comprises forming a supersaturated solution of said mixture, adding poly-(N^c-acryloyl-L-lysine) or poly-(N^c-methacryloyl-L-lysine) or poly-[L- α -glutamyl-(N-acryloyl)hydrazide] as an inhibitor of the L-amino acid when D-amino acid is desired, or a similar additive in the D-form when L-form is desired, and crystallizing part of the compound from said supersaturated solution.

10 8. A process according to claim 7, wherein also seed crystals of the desired form of Glu.HCl are added during the crystallization step.

9. A process according to claim 7 or 8 whenever executed in a membrane-separated two-compartment system.

15 10. A process according to any of claims 1 to 6, for resolution of a mixture of D- and L-forms of asparagine, which comprises forming a supersaturated solution of said mixture, adding polymer-bound L-lysine as crystallization inhibitor of the L-form of asparagine when the D-form of asparagine is desired, or including the D-form of these polymers when the L-form of asparagine is desired, and crystallizing a portion of the asparagine from said supersaturated solution.

20 11. A process according to claim 10, where, in addition seeds of asparagine of the desired form are added to said supersaturated solution.

12. A process according to any of claims 1 to 6 for the resolution of a mixture of D- and L-form of threonine which comprises forming a supersaturated solution of said mixture adding polymer bound L-lysine as crystallization inhibitor of the L-form of threonine when the D-form of threonine is desired, or including the D-form of the polymer when the L-form of threonine is desired, and crystallizing a portion of the threonine from said supersaturated solution.

25 13. A process according to claim 12, where in addition seeds of threonine of the desired form are added to said supersaturated solution.

14. A process according to any of claims 1 to 6, for resolution of a mixture of D- and L-Histidine HCl which comprises forming a supersaturated solution of said mixture, adding polymer bound L-lysine or polymer bound p-amino-L-phenyl alanine or polymer bound L-p-tyrosine as an inhibitor of the L-amino acid when the D-amino acid is desired or a similar polymeric additive in the D-form when the L-form is desired, and crystallizing part of the compound from said supersaturated solution, at a temperature of 45°C or above.

30 15. A process according to claim 2, for resolution of a mixture of D- and L- Histidine HCl which comprises forming a supersaturated solution of said mixture, adding polymer bound p-amino-L-phenyl alanine or polymer bound L-p-tyrosine as an inhibitor of L-amino acid when the D-amino acid is desired or a similar polymeric additive in D-form when the L-form is desired, and crystallizing part of the compound from said supersaturated solution at a temperature of 45°C or below.

35 16. A process according to any of claims 14 or 15, wherein also seed crystals of the desired form of His.HCl.H₂O are added during the crystallization step.

17. A process according to any of claim 1 to 6, for a resolution of a mixture of D and L-pHPGpTS which comprises forming a supersaturated solution of said mixture, adding polymer bound L-lysine or polymer bound p-amino-L-phenyl alanine or polymer bound L-p-tyrosine as an inhibitor of the L-amino acid when the D-amino acid is desired, or a similar polymeric additive in the D-form when the L-form is desired, and crystallizing part of the compound from said supersaturated solution.

40 18. A process according to claim 17, wherein also seed crystals of the desired form of pHPGpTS are added during the crystallization step.

19. A process according to any of claims 1 to 6, for resolution of a mixture of D-and L-forms of 3,5-dinitro-sec-phenethylbenzoate, which comprises forming a supersaturated solution of said mixture, adding poly-[N^c-acryloyl-(p-aminobenzoyl)-D-sec-phenethylamide] or the methacryloyl analogue as crystallization inhibitor of D-form of 3,5-dinitro-sec-phenethylbenzoate when L-form is desired, or including the L-forms of these polymers when D-form of 3,5-dinitro-sec-phenethylbenzoate is desired and crystallizing a portion from said supersaturated solution.

45 20. A process according to any of claims 7, 10, 12, 14, 17 or 19, where the polymer bound form used is poly-(N^c-acryloyl) lysine or poly-(N^c-methacryloyl)-L-lysine or a corresponding polymer, as defined in the specific claims.

21. Chiral soluble polymers for use in the resolution according to claim 1, of racemic mixtures of enantiomers, containing a specific entity which retards the crystallization of one of the enantiomers.

50 22. A chiral soluble polymer according to claim 21, of the form of poly-(N^c-acryloyl-L- or D-amino acid) or poly-(N^c-methacryloyl-L- or D-amino acid), where said amino acid is adapted to retard the crystallization of one of the enantiomers of the mixture to be resolved.

Revendications

1. Procédé de résolution cinétique de mélanges racémiques D,L de composés cristallisant sous forme de conglomerats à partir de solutions sursaturées de ces mêmes composés, qui comprend la réalisation de la cristallisation en présence d'une quantité effective d'un inhibiteur de cristallisation d'une des formes, cet inhibiteur étant lié à un polymère, puis la poursuite de la cristallisation préférentielle de l'autre forme.

2. Procédé conforme à la revendication 1, dans lequel la forme conglomerat est métastable et dans laquelle le polymère est également un inhibiteur de la forme racémique stable.

3. Procédé conforme aux revendications 1 ou 2, dans lequel le mélange D, L racémique est celui d'un acide aminé.

4. Procédé conforme aux revendications 1,2 ou 3, dans lequel l'inhibiteur, un acide aminé lié à un polymère, est l'un des énantiomères du mélange racémique à séparer, une modification chimique de ce dernier, ou une autre fraction connue pour inhiber la cristallisation de l'un des énantiomères.

5. Procédé conforme à l'une des revendications 1 à 4, dans lequel le polymère est un poly-N- ϵ -acryloyle ou un poly-N- ϵ -méthacryloyle, auquel est liée la fraction inhibitrice.

6. Procédé conforme à l'une des revendications 1 à 5, dans lequel on réalise la séparation dans un système comprenant deux compartiments séparés par une membrane perméable aux constituants du racémate, mais imperméable aux polymères sur lesquels sont fixés les groupes actifs, procédé dans lequel on place un inhibiteur de cristallisation de la forme L dans un compartiment, et un inhibiteur de cristallisation de la forme D dans l'autre compartiment, ces inhibiteurs étant des groupes actifs, fixés sur des polymères.

7. Procédé conforme à l'une des revendications 1 à 6, pour la résolution d'un mélange de chlorhydrates d'acide D-glutamique et d'acide L-glutamique, comprenant la formation d'une solution sursaturée dudit mélange, l'addition de poly-(N- ϵ -acryloyl-L-lysine) ou de poly-(N- ϵ -méthacryloyl-L-lysine) ou de poly-[L- α -glutamyle(N-acryloyl)hydrazide] comme inhibiteur de la forme L de l'acide aminé, lorsqu'on désire obtenir la forme D, ou un additif semblable de forme D, lorsqu'on désire obtenir la forme L, et la cristallisation partielle du composé à partir de ladite solution sursaturée.

8. Procédé conforme à la revendication 7, dans lequel on ajoute également des cristaux d'ensemencement de la forme de Glu.HCl désirée, pendant l'étape de cristallisation.

9. Procédé conforme à la revendication 7 ou 8, dans lequel la séparation est effectuée dans un système à deux compartiments séparés par une membrane.

10. Procédé conforme à l'une des revendications 1 à 6, pour la résolution d'un mélange des formes D et L de l'asparagine, qui comprend la formation d'une solution sursaturée de ce mélange, l'addition de L-lysine liée à un polymère, comme inhibiteur de cristallisation de la forme L de l'asparagine, lorsqu'on désire la forme D de l'asparagine, ou l'addition de la forme D de ces polymères, lorsqu'on désire la forme L de l'asparagine, et la cristallisation d'une partie de l'asparagine à partir de la dite solution sursaturée.

11. Procédé conforme à la revendication 10, dans lequel on ajoute en plus un ensemencement en asparagine de la forme désirée, à ladite solution sursaturée.

12. Procédé conforme à l'une des revendications 1 à 6, pour la résolution de mélanges de formes D et L de la thréonine, qui comprend la formation d'une solution sursaturée dudit mélange, l'addition de L-lysine fixée sur un polymère comme inhibiteur de la forme L de la thréonine, lorsqu'on désire la forme D de la thréonine, ou l'addition de la forme D du polymère lorsqu'on désire la forme L de la thréonine, et la cristallisation d'une partie de la thréonine à partir de ladite solution sursaturée.

13. Procédé conforme à la revendication 12, dans lequel on ajoute, à la solution sursaturée, un ensemencement de thréonine de la forme désirée.

14. Procédé conforme à une des revendications 1 à 6, pour la résolution d'un mélange de chlorhydrates de D et L histidine, qui comprend la formation d'une solution sursaturée dudit mélange, l'addition de L-lysine liée à un polymère ou de p-amino-L-phénylalanine liée à un polymère, ou de L-p-tirosine liée à un polymère, comme inhibiteur de l'acide aminé L, lorsqu'on désire obtenir l'acide aminé D, ou un additif polymère similaire de forme D, lorsqu'on désire la forme L, et la cristallisation d'une partie du composé à partir de ladite solution sursaturée, à une température de 45°C ou supérieure.

15. Procédé conforme à la revendication 2, pour la résolution d'un mélange de chlorhydrates de D et L histidine, qui comprend la formation d'une solution sursaturée dudit mélange, l'addition de p-amino-L-phénylalanine liée à un polymère ou de L-p-tirosine liée à un polymère comme inhibiteur de l'acide aminé L, lorsqu'on désire obtenir l'acide aminé D, ou d'un additif polymère analogue de forme D, lorsqu'on désire la forme L, et la cristallisation d'une partie du composé à partir de ladite solution sursaturée, à une température de 45°C ou inférieure.

16. Procédé conforme aux revendications 14 ou 15, dans lequel on ajoute également des cristaux d'ensemencement de la forme désirée de His.HCl.H₂O pendant l'étape de cristallisation.

17. Procédé conforme à l'une des revendications 1 à 6 pour la résolution d'un mélange de D et L-pHpGPTS, qui comprend la formation d'une solution sursaturée dudit mélange, l'addition de L-lysine liée à un polymère ou de p-amino-L-phénylalanine liée à un polymère, ou de L-p-tirosine liée à un polymère, comme inhibiteur de l'acide aminé L lorsqu'on désire obtenir l'acide aminé D, ou d'un additif polymère analogue de configuration D lorsqu'on désire la forme L, et la cristallisation d'une partie du composé à partir de ladite solution sursaturée.

18. Procédé conforme à la revendication 17, dans lequel on ajoute des cristaux d'ensemencement de la forme désirée de pHpGPTS au cours de l'étape de cristallisation.

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19. Procédé conforme à l'une des revendications 1 à 6, pour la résolution d'un mélange des formes D et L du dinitro-3,5-benzoate de sec-phénéthyle, qui comprend la formation d'une solution sursaturée dudit mélange, l'addition de poly-[N-acryloyl-(p-aminobenzoyl)-D-sec-phénéthylamide] ou du polymère méthacrylique correspondant, comme inhibiteur de cristallisation de la forme D du dinitro-3,5-benzoate de sec-phénéthyle, lorsqu'on désire obtenir la forme L, ou l'addition de la forme L de ces polymères, lorsqu'on désire obtenir la forme D du dinitro-3,5-benzoate de sec-phénéthyle, et la cristallisation d'une partie de ladite solution sursaturée.

5 20. Procédé conforme à l'une des revendications 7, 10, 12, 14, 17 ou 19, dans lequel le polymère utilisé est le poly-(N- ϵ -acryloyl) lysine ou le poly-(N- ϵ -méthacryloyl)-L-lysine ou un polymère correspondant tel que défini dans les revendications spécifiques.

10 21. Polymères solubles chiraux, pour emploi dans la résolution de mélanges racémiques d'énanthiomères, conformément à la revendication 1, contenant une entité spécifique qui retarde la cristallisation de l'un des énanthiomères.

15 22. Polymère soluble, chiral, conforme à la revendication 21, de la forme du poly-(N- ϵ -acryloyl-aminoacide L ou D) ou poly-(N- ϵ -méthacryloyl-aminoacide L ou D), dans lequel ledit acide aminé est adapté pour retarder la cristallisation de l'un des énanthiomères du mélange à séparer.

20 Patentansprüche

1. Verfahren zur kinetischen Spaltung razemischer D,L-Mischungen von Verbindungen, die in Form von Konglomeraten aus ihren übersättigten Lösungen kristallisieren, dadurch gekennzeichnet, daß die Kristallisation in Gegenwart einer wirksamen Menge eines polymergebundenen Kristallisationshemmers der einen Form vorgenommen wird, der somit die bevorzugte Kristallisation der anderen Form fördert.

25 2. Verfahren nach Anspruch 1, wobei das Konglomerat metastabil und das Polymer ein Hemmer der stabilen razemischen Form ist.

3. Verfahren nach Anspruch 1 oder 2, wobei die razemische D,L-Mischung die einer Aminosäure ist.

4. Verfahren nach den Ansprüchen 1, 2 oder 3, wobei der Hemmer, eine polymergebundene Aminosäure, eines der Enantiomeren der zu trennenden razemischen Mischung, eine chemische Modifikation davon oder eine andere Einheit ist, die bekannt ist, die Kristallisation eines der Enantiomeren zu hemmen.

30 5. Verfahren nach einem der Ansprüche 1 bis 4, wobei das Polymer ein Poly-N- ϵ -acryloyl- oder ein Poly-N- ϵ -methacryloyl-Polymer darstellt, mit dem die hemmende Einheit verbunden ist.

6. Verfahren nach einem der Ansprüche 1 bis 5, durchgeführt in einer Anordnung aus zwei Zellen, die durch eine für die Bestandteile des Razemats durchlässige, jedoch für die polymergebundenen Einheiten undurchlässige Membran getrennt sind, wobei in der einen Zelle der Kristallisationshemmer der L-Form, in der anderen der der D-Form vorliegt, und die Hemmer dabei polymergebundene hemmende Einheiten sind.

35 7. Verfahren nach einem der Ansprüche 1 bis 6 zur Spaltung einer Mischung aus D- und L-Glutaminsäure-hydrochlorid, dadurch gekennzeichnet, daß man eine übersättigte Lösung der Mischung bildet, zur Gewinnung der D-Aminosäure Poly-(N- ϵ -acryloyl-L-lysin) oder Poly-(N- ϵ -methacryloyl-L-lysin) oder Poly-[L- α -glutamyl-(N- ϵ -acryloyl)-hydrazid] als Hemmer der L-Aminosäure zusetzt, oder zur Gewinnung der L-Form das entsprechende Additiv in der D-Form zusetzt, und den entsprechenden Teil der Verbindung aus der übersättigten Lösung kristallisieren läßt.

40 8. Verfahren nach Anspruch 7, wobei Impfkristalle der gewünschten Glutaminsäure-hydrochlorid-Form während der Kristallisation zugesetzt werden.

9. Verfahren nach Anspruch 7 oder 8, dadurch gekennzeichnet, daß es in einer durch eine Membran getrennten Zwei-Zellen-Anordnung durchgeführt wird.

45 10. Verfahren nach einem der Ansprüche 1 bis 6 zur Spaltung einer Mischung der D- und L-Form von Asparagin, dadurch gekennzeichnet, daß man eine übersättigte Lösung der Mischung bildet, zur Gewinnung der D-Form von Asparagin polymergebundenes L-Lysin als Kristallisationshemmer der L-Form von Asparagin zusetzt oder zur Gewinnung der L-Form von Asparagin die D-Form dieser Polymere zusetzt und den entsprechenden Teil des Asparagins aus der übersättigten Lösung kristallisieren läßt.

11. Verfahren nach Anspruch 10, wobei Impfkristalle von Asparagin in der gewünschten Form der übersättigten Lösung zugesetzt werden.

50 12. Verfahren nach einem der Ansprüche 1 bis 6 zur Spaltung einer Mischung der D- und L-Form von Threonin, dadurch gekennzeichnet, daß man eine übersättigte Lösung dieser Mischung bildet, zur Gewinnung der D-Form von Threonin polymergebundenes L-Lysin als Kristallisationshemmer der L-Form von Threonin zusetzt oder zur Gewinnung der L-Form von Threonin die D-Form dieses Polymers zusetzt und den entsprechenden Teil des Threonins aus der übersättigten Lösung kristallisieren läßt.

60 13. Verfahren nach Anspruch 12, wobei Impfkristalle von Threonin in der gewünschten Form der übersättigten Lösung zugesetzt werden.

14. Verfahren nach einem der Ansprüche 1 bis 6 zur Spaltung einer Mischung von D- und L-Histidin HCl, dadurch gekennzeichnet, daß man eine übersättigte Lösung dieser Mischung bildet, zur Gewinnung der D-Aminosäure polymergebundenes L-Lysin oder polymergebundenem P-Amino-L-phenylalanin oder polymergebundenem L-p-Tyrosin als Hemmer der L-Aminosäure zusetzt oder zur Gewinnung der L-Form ein

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entsprechendes polymeres Additiv der D-Form zusetzt und den entsprechenden Teil der Verbindung aus der übersättigten Lösung bei einer Temperatur von 45°C oder darüber kristallisieren läßt.

15. Verfahren nach Anspruch 2 zur Spaltung einer Mischung von D- und L-Histidin HCl, dadurch gekennzeichnet, daß man eine übersättigte Lösung dieser Mischung bildet, zur Gewinnung der D-Aminosäure polymergebundenes p-Amino-L-phenylalanin oder polymergebundenes L-p-Tyrosin als Hemmer der L-Aminosäure zusetzt oder zur Gewinnung der L-Form ein entsprechendes polymeres Additiv der D-Form zusetzt und den entsprechenden Teil der Verbindung aus der übersättigten Lösung bei einer Temperatur von 45°C oder darunter kristallisieren läßt.

16. Verfahren nach den Ansprüchen 14 oder 15, wobei Impfkristalle von Histidin-hydrochlorid-monohydrat in der gewünschten Form während der Kristallisationsstufe zugesetzt werden.

17. Verfahren nach einem der Ansprüche 1 bis 6 zur Spaltung einer Mischung von D- und L-pHPGpTS, dadurch gekennzeichnet, daß man eine übersättigte Lösung dieser Mischung bildet, zur Gewinnung der D-Aminosäure polymergebundenes L-Lysin, polymergebundenes p-Amino-L-phenylalanin oder polymergebundenes L-p-Tyrosin als Hemmer der L-Aminosäure zusetzt oder zur Gewinnung der L-Form ein entsprechendes polymeres Additiv der D-Form zusetzt und den entsprechenden Teil der Verbindung aus der übersättigten Lösung kristallisieren läßt.

18. Verfahren nach Anspruch 17, wobei Impfkristalle von pHPGpTS in der gewünschten Form während der Kristallisationsstufe zugesetzt werden.

19. Verfahren nach einem der Ansprüche 1 bis 6 zur Spaltung einer Mischung der D- und L-Form von 3,5-Dinitro-sec-phenäthylbenzoat, dadurch gekennzeichnet, daß man eine übersättigte Lösung dieser Mischung bildet, zur Gewinnung der L-Form Poly-[N-acryloyl-(p-aminobenzoyl)-D-sec-phenäthylamid] oder das Methacryloyl-Analoge als Kristallisationshemmer der D-Form von 3,5-Dinitro-sec-phenäthylbenzoat zusetzt oder zur Gewinnung der D-Form von 3,5-Dinitro-sec-phenäthylbenzoat die L-Form dieser Polymere, und den entsprechenden Teil aus der übersättigten Lösung kristallisieren läßt.

20. Verfahren nach einem der Ansprüche 7, 10, 12, 14, 17 oder 19, wobei die verwendete polymergebundene Form Poly-(N^c-acryloyl)-lysin, Poly-(N^c-methacryloyl)-L-lysin oder ein entsprechendes Polymer, wie in den einzelnen Ansprüchen beschrieben, ist.

21. Chirale lösliche Polymere zur Verwendung bei der Spaltung von razemischen Gemischen von Enantiomeren nach Anspruch 1, die eine bestimmte Einheit enthalten, die die Kristallisation eines der Enantiomere verzögert.

22. Ein chirales lösliches Polymer nach Anspruch 21 in der Form von Poly-(N^c-acryloyl-L- oder D-aminoäure) oder Poly-(N^c-methacryloyl-L- oder D-aminoäure), wobei die Aminosäure die Kristallisation eines der Enantiomere der zu trennenden Mischung verzögert.

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